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One Pot Synthesis of Highly Functionalized Tetrahydropyridines Using Nano-$TiCl_2$/cellulose as Biodegradable and Eco-Friendly Catalyst

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Nano-$TiCl_2$/cellulose was used as an efficient and biodegradable Lewis acid catalyst for the synthesis of highly functionalized tetrahydropyridines by one-pot multicomponent reactions of amines and aldehydes with β-ketoester. The catalyst was prepared *via* reaction of nano-cellulose and $TiCl_4$ and characterized by Fourier transform infrared spectroscopy (FT-IR), field emission scanning electron microscopy (FESEM), powder X-ray diffraction (XRD), energy dispersive X-ray spectroscopy (EDX), X-ray fluorescence techniques (XRF) and transmission electron microscopy (TEM). Simple methodology, eco-friendly catalyst, clean procedure, easy work-up and high yields are some of the important advantages of this protocol.

Keywords: Nano-$TiCl_2$/cellulose, Tetrahydropyridines, Nano-cellulose, Lewis acid catalyst, biodegradable catalyst

INTRODUCTION

Tetrahydropyridines (THPs) and their derivatives have potent pharmaceutical properties as antiemetic and antipsychotic agents [1,2], anticancer [3,4] and antimalarial [5]. THPs have been used as drugs in the treatment of diseases such as alzheimer (GTS-21) [6] and central nervous system (CNS) disorders (RO-10-5824) [7,8]. Alkyl-1-aryl-4-(arylamino)-2,6-di-aryl-1,2,5,6-tetrahydro-pyridine-3-carboxylates are some important densely substituted tetrahydropyridines. These compounds are synthesized *via* one-pot reaction of *p*-substituted anilines, *p*-substituted aldehydes and alkyl acetoacetate. Recently, these compounds have been synthesized in the presence of $InCl_3$ [9,10], BDMS [11], L-proline/TFA [5], TBATB [12], I_2 [13], CAN [14], $ZrOCl_2{\cdot}8H_2O$ [15], $ZrCl_4$ [3], *p*-$TsOH{\cdot}H_2O$ [16], $Fe(NO_3)_3{\cdot}9H_2O$ [17], $FeCl_3/SiO_2$ [18], amberlite IRA400-Cl resin/I_2/KI [19], HOAc [20], $BF_3.SiO_2$ [21], nano-silica sulfuric acid [22], $NiFe_2O_4@SiO_2$ [23] and BF_3 [24].

Considering the new trends of science and technology towards using natural materials such as cellulose, the research efforts on green and eco-friendly methods have become popular and desirable. Cellulose is one of the most abundant natural carbon based biopolymers containing free OH groups with nucleophilic character. Cotton is a natural, cheap and readily available source of cellulose. In this work, we have investigated preparation of nano-cellulose from cotton and synthesis of nano-$TiCl_2$/cellulose by bonding $TiCl_4$ to OH groups of D-glucose units in nano-cellulose.

Herein, we introduce nano-$TiCl_2$/cellulose as a new, biodegradable, inexpensive and eco-friendly bio-based catalyst for the synthesis of alkyl-1-aryl-4-(arylamino)-2,6-di-aryl-1,2,5,6-tetrahydropyridine-3-carboxylates.

EXPERIMENTAL

Apparatus and Analysis

All compounds were purchased from Merck chemical company and used without any additional purification. A

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refrigerated centrifuge (Appendorf Centrifuge 5417R) was used for preparation of nano-cellulose. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ^{1}H NMR and ^{13}C NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected. X-ray diffraction pattern was obtained by PAN alytical X'Pert Pro MPD, powered by a Philips PW3040/60 X-ray generator and fitted with an X'Celerator detector and a Cu Kα anode (λ = 1.5418 Å) in the 2θ range from 5-80°. Field emission scanning electron microscopy (FESEM) was obtained on a Mira 3-XMU. Elemental analysis were performed using Costech ECS 4010 CHNS-O analyzer. Quantitative elemental information (EDS) of nano-$TiCl_2$/cellulose was measured by EDS instrument, Phenom pro X. Optical rotation was determined by OGAW Polarimeter (OSK 7822). XRF analysis was carried out using BRUKER, S4 EXPLORER instrument.

Preparation of nano-cellulose from cotton. Cotton fibers were washed with distilled water several times and dried in an air-circulated oven at 100 ± 2 ℃ until constant weight. Then, they were chopped to an approximate length of 5-10 mm. The fibers were then treated with a 17.5 w/v NaOH solution at 100 °C for 12 h under mechanical stirring. This treatment allowed purifying cellulose by removing other constituents like lignin, hemicellulose, wax, organic acids, *etc*. present in the fibres.

Subsequently, fibres were filtered and washed with distilled water until the alkali was completely eliminated. It was then bleached with 100 ml of 1:1 dilution of 3.5% w/v sodium hypochlorite solution at 80 °C for 3 h under mechanical stirring. The resulting alpha cellulose was hydrolyzed partially using 65% sulfuric acid aqueous solution with a cotton-to-acid weight ratio of 1-10 at 45 ℃. After 1 h, the obtained suspension was diluted with water five-fold to stop the hydrolysis reaction. The suspension was centrifuged at 12,000 rpm to separate nano-cellulose from acid solution. Washing with water and centrifuging were repeated four to five times to remove any remaining free acid.

Preparation of Nano-$TiCl_2$/cellulose

In a well-ventilated system, $TiCl_4$ (5 ml) was added dropwise to the mixture of nano-cellulose (5 g) in chloroform (20 ml). The mixture was stirred for one hour at room temperature. The resulted suspension was filtered, washed with chloroform and dried at room temperature.

General Procedure for Synthesis of THPs

Firstly, a mixture of para-substituted anilines (2 mmol) and ethyl acetoacetate (1 mmol) was heated while stirring at 80 °C for 30 min in the presence of nano-$TiCl_2$/cellulose (0.03 g). Then, the para-substituted benzaldehyde (2 mmol) was added and the final mixture was heated at 80 ℃. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was dissolved into hot ethanol and filtered off for separation of catalyst. By adding water to filtrate, the product was appeared as a pure solid in high yields.

Spectral Data Analysis for Compounds

Ethyl-1-phenyl-4-(phenylamino)-2,6-bis(4-bromophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_a): Pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.29 (s, 1H, NH), 7.4 (br, s, 4H, Ar-H), 7.17 (m, 5H, Ar-H), 7.1 (br, s, 2H, Ar–H), 7.01 (br, s, 2H, Ar-H), 6.66 (br, s, 1H, Ar-H), 6.44 (br, s, 4H, Ar-H), 6.34 (br, s, 1H), 5.08 (s, 1H, H-6), 4.44 (br, s, 1H, O$\underline{CH_2}$), 4.33 (br, s, 1H, O$\underline{CH_2}$), 2.79 (m, 2H, H-5,5´), 1.45 (br, s, 3H, OCH$_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.99, 155.85, 146.47, 143.03, 141.50, 137.66, 131.75, 131.39, 129.11, 129.06, 128.46, 128.18, 126.00, 125.73, 120.97, 120.26, 116.80, 112.98, 97.72, 59.93, 57.45, 54.78, 33.68, 14.84. IR: 3338, 2894, 1651, 1594, 1500, 1248, 1061, 748, 692. m.p.: 218-220 ºC.

Ethyl-1-(4-tolyl)-4-(4-tolylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-arboxylate (Table 4, IV_b): Cream solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.22 (s, 1H, NH), 7.27-7.35 (m, 8H, Ar-H), 7.20 (m, 2H, Ar-H), 6.90 (m, 4H, Ar-H), 6.44 (br, s, 3H, Ar-H, H-2), 6.16 (br, s, 2H, Ar-H), 5.12 (s, 1H, H-6), 4.45 (m, 1H, OCH_2), 4.33 (m, 1H, OCH_2), 2.85 (dd, 1H, ^{2}J = 15 Hz ^{3}J = 5.6 Hz, H-5), 2.74 (d, 1H, ^{2}J = 15Hz, H-5´), 2.26 (s, 3H, Ar-$\underline{CH_3}$), 2.16 (s, 3H, Ar-$\underline{CH_3}$), 1.46 (t, 3H, OCH$_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.32, 156.47, 144.87, 144.39, 143.06, 135.56, 135.24, 129.47, 129.43, 128.63, 128.22, 127.06, 126.68, 126.46, 126.20, 125.96, 125.05, 112.90, 97.70, 59.58, 58.25, 55.18, 33.58, 20.91, 20.16, 14.85. IR: 3238, 3025, 2921,

1650, 1599, 1514, 1450, 1365, 1315, 1247, 1069, 700. m.p.: 193-194 ºC.

Ethyl-1-(4-tolyl)-4-(4-tolylamino)-2,6-bis(4-bromophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_c). Pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.21 (s, 1H, NH), 7.39 (d, 5H, ^3J = 7.6 Hz, Ar-H), 7.19 (d, 2H, ^3J = 7.6 Hz, Ar-H), 7.00 (d, 2H, ^3J = 7.6 Hz, Ar-H), 6.96 (d, 2H, ^3J = 7.6 Hz, Ar-H), 6.89 (d, 2H, ^3J = 7.6 Hz, Ar-H), 6.36 (br, d, 2H, ^3J = 7.6 Hz, Ar-H, H-2), 6.29 (br, s, 2H, Ar-H), 5.04 (s, 1H, H-6), 4.44 (m, 1H, OCH_2), 4.33 (m, 1H, OCH_2), 2.75 (m, 2H, H-5,5´), 2.29 (s, 3H, Ar-$\underline{CH_3}$), 2.18 (s, 3H, Ar-$\underline{CH_3}$), 1.44 (t, 3H, ^3J = 6.4 Hz, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 156.1, 144.3, 143.3, 141.8, 141.9, 135.9, 135.0, 131.7, 131.3, 129.6, 128.5, 128.2, 125.88, 125.82, 120.8, 120.1, 113.0, 97.2, 59.7, 57.4, 54.9, 33.6, 20.9, 20.2, 14.8. IR: 3372, 2977, 2917, 2874, 1651, 1599, 1514, 1485, 1363, 1244, 1067, 1009, 826. m.p.: 215-217 ºC. Anal. Calcd. for $C_{34}H_{32}Br_2N_2O_2$: C, 62.87; H, 4.80; N, 4.44. Found: C, 59.68; H, 4.74; N, 4.13.

Ethyl-1-(4-ethylphenyl)-4-((4-ethylphenyl)amino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_d): White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.23 (s, 1H, NH), 7.26 (m, 6H, Ar-H), 7.08 (d, 2H, ^3J = 7.6 Hz, Ar-H), 6.98 (d, 2H, ^3J = 7.6 Hz, Ar-H), 6.92 (d, 2H, ^3J = 7.6 Hz, Ar-H), 6.38 (d, 2H, ^3J = 7.6 Hz, Ar-H), 6.31 (m, 3H, Ar-H), 5.07 (s, 1H, H-6), 4.43 (m, 1H, OCH_2), 4.35 (m, 1H, OCH_2), 2.82-2.75 (m, 2H, H-5,5´), 2.59 (q, 2H, ^3J = 7.5 Hz, Ar-$\underline{CH_2}CH_3$), 2.49 (q, 2H, ^3J = 7.6 Hz, Ar-$\underline{CH_2}CH_3$), 1.45 (t, 3H, ^3J = 6.8 Hz, $OCH_2\underline{CH_3}$), 1.20 (t, 3H, ^3J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$), 1.14 (t, 3H, ^3J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 156.2, 144.6, 142.9, 142.2, 141.3, 135.2, 132.8, 132.2, 132.1, 128.4, 128.1, 127.9, 125.9, 113.1, 97.3, 59.7, 57.5, 54.9, 33.7, 28.3, 27.6, 15.7, 15.5, 14.8. IR: 3226, 2972, 1648, 1600, 1514, 1486, 1409, 1368, 1316, 1253, 1069, 811. m.p.: 209-211 ºC. Anal. Calcd. for $C_{36}H_{36}Cl_2N_2O_2$: C, 72.11; H, 6.05; N, 4.67. Found: C, 70.95; H, 6.38; N, 4.58.

Ethyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_e): Pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.25 (s, 1H, NH), 7.31-7.23 (m, 8H, Ar-H), 7.17 (d, 2H, ^3J = 7.2 Hz, Ar-H), 7.06 (d, 2H, ^3J = 8.4 Hz, Ar-H), 7.01 (d, 2H, ^3J = 8.4 Hz, Ar-H), 6.44 (d, 2H, ^3J = 8.6 Hz, Ar-H), 6.40 (s, 1H, H-2), 6.18 (d, 2H, ^3J = 8.6 Hz, Ar-H), 5.11 (d, ^3J = 4.4 Hz, 1H, H-6), 4.49 (m, 1H, $OC\underline{H_2}$), 4.35 (m, 1H, $OC\underline{H_2}$), 2.86 (dd, 1H, ^2J = 15.2 Hz, ^3J = 5.6 Hz, H-5), 2.71 (d, 1H, ^2J = 15.2 Hz, H-5´), 1.46 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.15, 159.93, 155.41, 145.50, 143.07, 141.24, 139.36, 139.00, 138.50, 131.43, 129.98, 129.17, 128.31, 127.52, 127.03, 127.00, 126.52, 97.25, 60.32, 59.48, 55.27, 33.49, 13.73. IR: 3370, 2983, 1656, 1603, 1493, 1452, 1396, 1365, 1245, 1072, 803, 746, 696. m.p.: 202-204 ºC.

Ethyl-1,2,6-tris(4-chlorophenyl)-4-((4-chlorophenyl) amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_f). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.17 (1 H, s, NH), 7.11-7.19 (m, 6H, Ar-H), 7.03-7.06 (m, 2H, Ar-H), 6.92-6.97 (m, 4H, Ar-H), 6.30 (s, 1H, H-2), 6.26 (d, 2H, ^3J = 3.9 Hz, Ar-H), 6.22 (d, 2H, ^3J = 6.6 Hz, Ar-H), 4.98 (br s, 1H, H-6), 4.33-4.43 (m, 1H, $OC\underline{H_2}$), 4.19-4.30 (m, 1H, $OC\underline{H_2}$), 2.74 (dd, 1H, ^2J = 15 Hz, ^3J = 5.4 Hz, H-5), 2.6 (dd, 1H, ^2J = 15 Hz, ^3J = 2.4 Hz, H-5´), 1.38 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.89, 155.16, 145.02, 141.69, 140.37, 136.18, 133.22, 132.42, 131.63, 129.21, 128.97, 128.91, 128.57, 127.90, 127.69, 126.87, 121.86, 114.09, 98.24, 60.14, 57.45, 54.88, 33.59, 14.79. IR: 3363, 3241, 2978, 1654, 1491, 1243, 1091, 821.

Ethyl-1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_g). Cream solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.25 (s, 1H, NH), 7.40-7.10 (m, 8H, Ar-H), 6.33-6.28 (m, 7H, Ar-H, H-2), 5.06 (s, 1H, H-6), 4.50-4.40 (m, 1H, $OC\underline{H_2}$), 4.40-4.30 (m, 1H, $OC\underline{H_2}$), 2.81-2.72 (m, 1H, H-5), 2.66 (d, 1H, ^3J = 7.6 Hz, H-5´), 1.46 (s, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.89, 155.03, 145.46, 141.65, 140.28, 136.73, 133.28, 132.48, 132.21, 131.82, 129.00, 128.61, 127.91, 127.71, 127.14, 119.44, 114.65, 109.09, 98.40, 60.19, 57.44, 54.87, 33.62, 14.82. IR: 3064, 2976, 1621, 1591, 1566, 1488, 1403, 1364, 1244, 1167, 1070, 1011, 832, 711. m.p.: 193-195 ºC.

Ethyl-1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_h). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ 10.25 (s, 1H, NH), 7.22 (d, 2H, ^3J = 8 Hz, Ar-H), 7.18 (d, 2H, ^3J = 8.4 Hz, Ar-H), 7.13 (d, 2H, ^3J = 8.8 Hz, Ar-H), 6.83 (br, s, 4H, Ar-H), 6.39 (d, 2H, ^3J = 8.4 Hz, Ar-H), 6.29 (s, 1H, H-2), 6.19 (d, 2H, ^3J = 8 Hz, Ar-H), 5.04 (s, 1H, H-6), 4.50-4.40 (m, 1H, OCH_2), 4.40-4.30 (m, 1H,

OCH_2), 3.78 (s, 6H, OMe), 2.83 (br.d, 2H, ^3J = 7.6 Hz, H-5), 2.69 (d, 1H, ^3J = 7.6 Hz, H-5´), 1.46 (t, 3H, ^3J = 6.8 Hz , $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.22, 158.97, 158.26, 155.38, 146.03, 137.13, 135.10, 134.00, 132.06, 131.61, 127.44, 119.04, 114.67, 114.20, 113.76, 108.39, 99.05, 59.98, 57.66, 55.41, 54.74, 33.62, 14.85. IR: 3234, 2931, 2918, 2834, 1650, 1608, 1499, 1319, 1249, 1173, 1068, 802. m.p.: 217-219 ºC.

Ethyl-1-phenyl-4-(phenylamino)-2,6-di-4-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_i). Gray solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.30 (s, 1H, NH), 7.25 (m, 2H, Ar-H), 7.1 (m, 12H, Ar-H), 6.59 (m, 3H, Ar-H), 6.42 (br, s, 1H, H-2), 6.31 (br, s, 2H, Ar-H), 5.13 (s, 1H, H-6), 4.47 (m, 1H, OCH_2), 4.33 (m, 1H, $O\underline{CH_2}$), 2.86 (br, s, 1H, H-5), 2.79 (m, 1H, H-5´), 2.34 (s, 6H, Ar-$\underline{CH_3}$), 1.47 (m, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.31, 156.11, 147.11, 141.07, 139.72, 138.02, 136.62, 135.78, 129.29, 128.95, 128.88, 128.82, 126.58, 126.35, 125.77, 125.55, 115.98, 112.92, 98.37, 59.66, 57.98, 54.89, 33.68, 21.15, 21.06, 14.84. IR: 3234, 3028, 2981, 2921, 2868, 1650, 1594, 1500, 1370, 1325, 1254, 1174, 1068, 748, 695. m.p.: 228-230 ºC.

Ethyl-1-phenyl-4-(phenylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_j). Gray solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.30 (s, 1H, NH), 7.13 (m, 12H, Ar-H), 6.66 (br, s, 1H, Ar-H), 6.42 (m, 6H, Ar-H), 5.10 (s, 1H, H-6), 4.45 (br, s,1H, OCH_2), 4.33 (br, s, 1H, OCH_2), 2.79 (m, 2H, H-5,5´), 1.32 (br, s, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.01, 155.84, 146.51, 142.47, 140.95, 137.68, 132.88, 132.13, 129.08, 129.03, 128.80, 128.43, 128.05, 127.80, 125.97, 125.70, 116.75, 112.97, 97.79, 59.91, 57.40, 54.72, 33.72, 14.83. IR: 3376, 2979, 1650, 1503, 1500, 1365, 1240, 1168, 1053, 752, 695. m.p.: 202-204 ºC.

Ethyl-1,2,6-tri-4-tolyl-4-(4-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_k). Cream solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.22 (s, 1H, NH), 7.23 (m, 2H, Ar-H), 7.08 (m, 6H, Ar-H), 6.89 (m, 4H, Ar-H), 6.43 (m, 2H, Ar-H), 6.37 (s, 1H, H-2), 6.16 (m, 2H, Ar-H), 5.09 (br, s, 1H, H-6), 4.44 (m, 1H, $O\underline{CH_2}$), 4.33 (m, 1H, $O\underline{CH_2}$), 2.82 (dd, 1H, ^2J = 15 Hz , ^3J = 5.6 Hz, H-5), 2.73 (d, 1H, ^2J = 15 Hz, H-5´), 2.32 (s, 6H, Ar-$\underline{CH_3}$), 2.25 (s, 3H, Ar-$\underline{CH_3}$), 2.17 (s, 3H, Ar-$\underline{CH_3}$), 1.45 (t, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.38, 156.51, 154.01, 141.46, 140.00, 136.52, 135.69, 135.39, 129.44, 129.28, 128.93, 126.63, 126.40, 125.96, 124.87, 112.87, 97.84, 59.53, 57.97, 55.01, 21.17, 21.08, 20.93, 20.20, 14.87. IR: 3374, 2979, 2921, 1648, 1602, 1513, 1445, 1368, 1245, 1170, 1067, 821. m.p.: 170-172 ºC.

Ethyl-1-(4-ethylphenyl)-4-((4-ethylphenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_l). Cream solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.23 (s, 1H, NH), 7.35 (d, 3H, ^3J = 7.2 Hz, Ar-H), 7.29 (m, 4H, Ar-H), 7.21 (t, 2H, ^3J = 7.2 Hz, Ar-H), 6.91 (d, 4H, ^3J = 7.2 Hz, Ar-H), 6.46 (m, 3H, Ar-H), 6.17 (d, 2H, ^3J = 7.2 Hz, Ar-H), 5.14 (br, s, 1H, H-6), 4.46 (m, 1H, $O\underline{CH_2}$), 4.33 (m, 1H, $O\underline{CH_2}$), 2.85 (dd, 1H, ^2J = 15.2 Hz, ^3J = 5.6 Hz, H-5), 2.75 (d, 1H, ^2J = 15.2 Hz, H-5´), 2.56 (q, 2H, ^3J = 7.5 Hz, Ar-$\underline{CH_2}$), 2.47 (q, 2H, ^3J = 7.3 Hz, Ar-$\underline{CH_2}$), 1.47 (t, 3H, ^3J = 7.6 Hz, $OCH_2\underline{CH_3}$), 1.18 (t, 3H, ^3J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$), 1.12 (t, 3H, ^3J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 156.5, 145.1, 144.5, 143.2, 141.9, 135.5, 131.6, 128.6, 128.2, 127.1, 126.7, 126.5, 126.2, 126.0, 112.9, 97.8, 59.6, 58.4, 55.3, 33.6, 28.3, 27.6, 15.7, 15.5, 14.9. IR: 3348, 2963, 1650, 1592, 1514, 1451, 1372, 1314, 1248, 1067, 699. m.p.: 187-189 ºC. Anal. Calcd. for $C_{36}H_{38}N_2O_2$: C, 81.47; H, 7.22; N, 5.28. Found: C, 78.03; H, 6.96; N, 5.10.

Ethyl-1-(4-ethylphenyl)-4-((4-ethylphenyl)amino)-2,6-di-4-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_m). Cream solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.22 (s, 1H, NH), 7.23 (d, 2H, ^3J = 7.6 Hz, Ar-H), 7.08 (m, 6H, Ar-H), 6.92-6.90 (m, 4H, Ar-H), 6.46 (d, 2H, ^3J = 8.4 Hz, Ar-H), 6.38 (s, 1H, H-2), 6.19 (d, 2H, ^3J = 7.6 Hz, Ar-H), 5.09 (br, s, 1H, H-6), 4.44 (m, 1H, OCH_2), 4.30 (m, 1H, $O\underline{CH_2}$), 2.83 (dd, 1H, ^2J = 14.8 Hz, ^3J = 5.2 Hz, H-5), 2.74 (d, 1H, ^2J = 14.8 Hz, H-5´), 2.56 (q, 2H, ^3J = 7.2 Hz, Ar-$\underline{CH_2}$), 2.46 (q, 2H, ^3J = 7.2 Hz, Ar-$\underline{CH_2}$), 2.35 (s, 3H, Ar-$\underline{CH_3}$), 2.32 (s, 3H, Ar-$\underline{CH_3}$), 1.45 (t, 3H, ^3J = 6.8 Hz, $OCH_2\underline{CH_3}$), 1.18 (t, 3H, ^3J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$), 1.12 (t, 3H, ^3J = 7.6 Hz, Ar-$CH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 156.4, 145.2, 141.7, 141.5, 140.1, 136.4, 135.6, 135.5, 131.3, 129.2, 128.8, 128.1, 126.6, 126.4, 125.9, 112.8, 97.9, 59.5, 58.0, 55.0, 33.6, 28.2, 21.1, 21.0, 15.6, 15.4, 14.8. IR: 3372, 2964, 2928, 2871, 1651, 1601, 1514, 1454, 1367, 1248, 1171, 1068, 814. m.p.: 176-178 ºC. Anal. Calcd. for $C_{38}H_{42}N_2O_2$: C, 81.68; H, 7.58; N, 5.01. Found: C, 76.92; H, 7.37; N, 4.73.

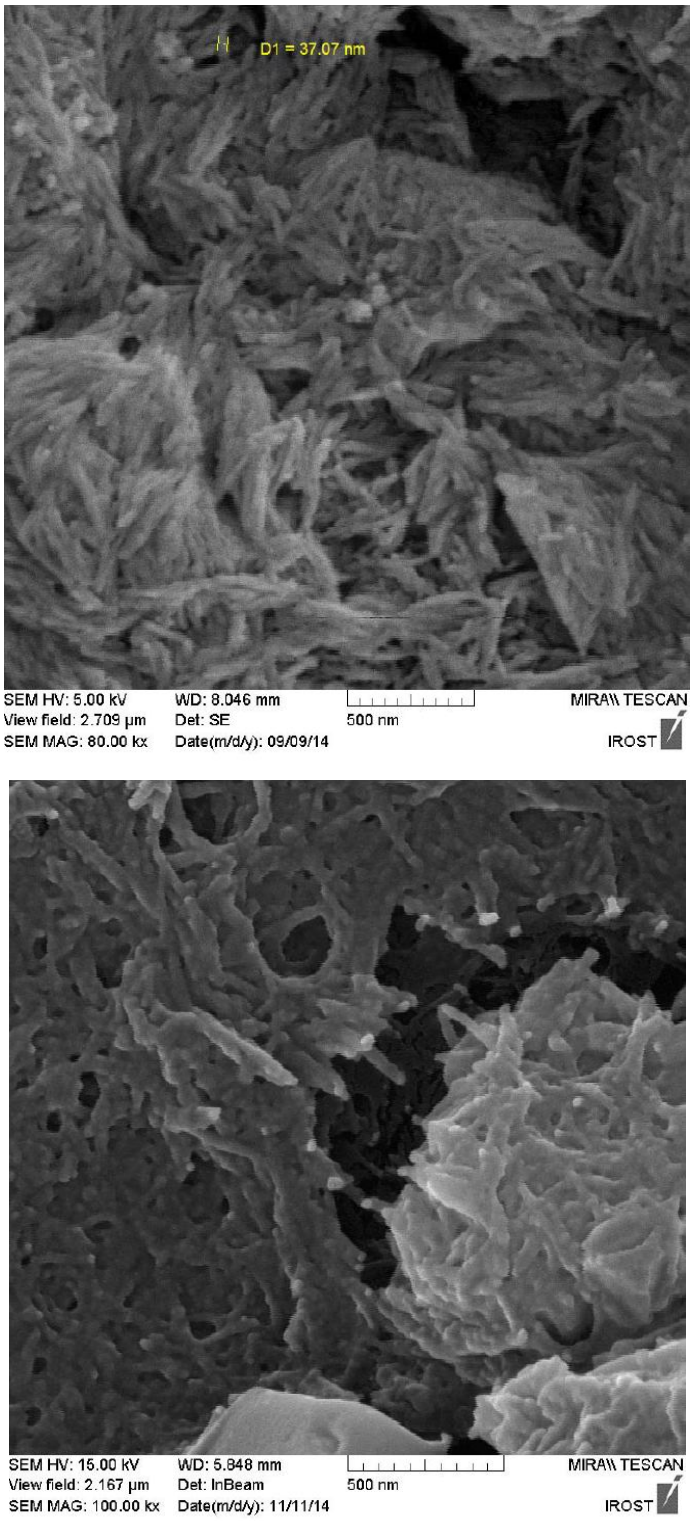


Fig. 1. (a) FESEM image of nano-cellulose, (b) FESEM of nano-$TiCl_2$/cellulose and (c) TEM of nano-$TiCl_2$/cellulose.

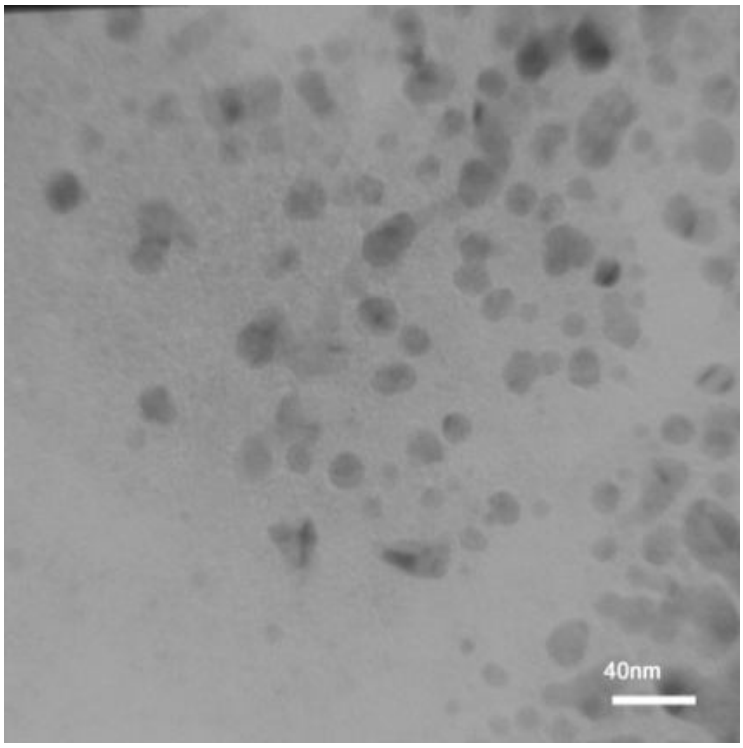


Fig. 1. Continued.

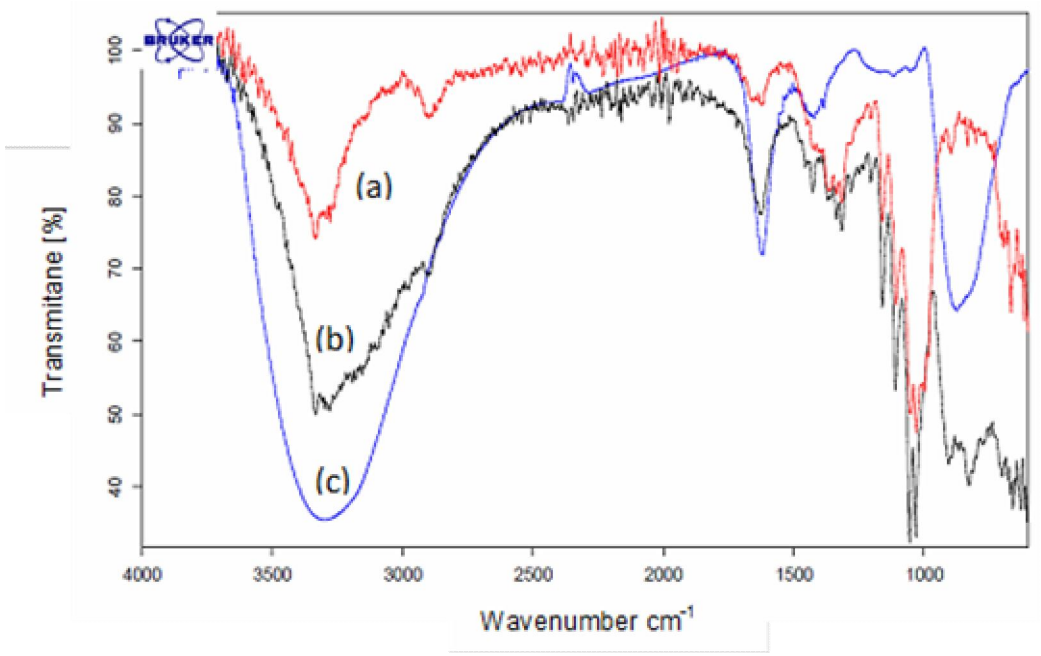


Fig. 2. FT-IR spectra of (a) nano-cellulose, (b) nano-$TiCl_2$/cellulose, and (c) $TiCl_4$.

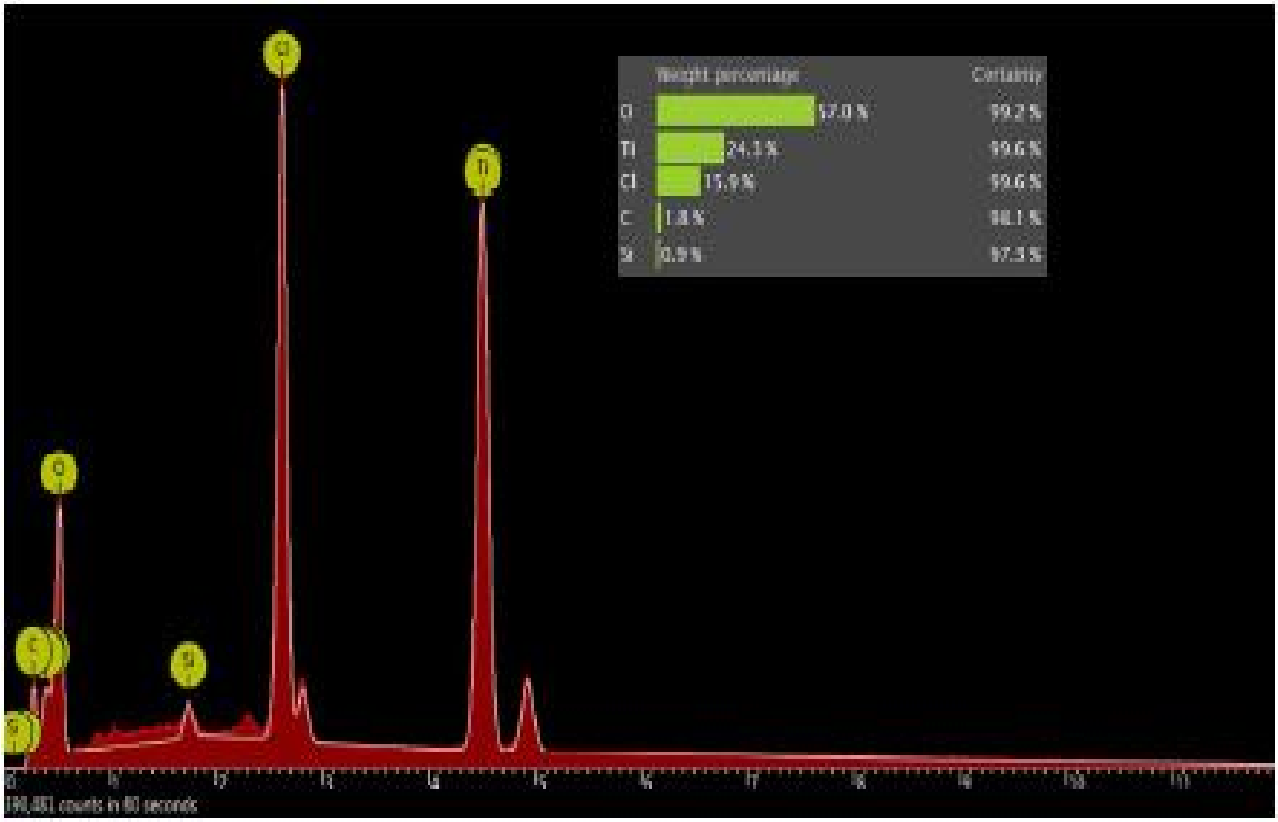


Fig. 3. EDS (EDX) spectra of nano-$TiCl_4$/cellulose.

Ethyl-1-(4-bromophenyl)-4-((4-bromophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Table 4, IV_n). Pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.25 (s, 1H, NH), 7.30-7.22 (m, 8H, Ar-H), 7.20 (d, 2H, ^3J = 8.0 Hz, Ar-H), 7.16 (d, 2H, ^3J = 8.4 Hz, Ar-H), 7.14 (d, 2H, ^3J = 8.4 Hz, Ar-H), 6.40 (d, 2H, ^3J = 7.2 Hz, Ar-H), 6.4 (s, H-2), 6.11 (d, 2H, ^3J = 8.0 Hz, Ar-H), 5.11 (d, 1H, ^3J = 4.4 Hz, H-6), 4.48 (dq, 1H, ^2J = 10.8 Hz, ^3J = 7.2 Hz, O$\underline{CH_2}$), 4.35 (dq, 1H, ^2J = 10.8 Hz, ^3J = 7.2 Hz, O$\underline{CH_2}$), 2.86 (dd, 1H, ^2J = 14.8 Hz, ^3J = 6.0 Hz, H-5), 2.71 (d, 1H, ^2J = 14.8 Hz, H-5′), 1.48 (t, 3H, ^3J = 7.2 Hz $OCH_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.18, 155.31, 145.93, 143.19, 142.17, 136.95, 132.02, 131.64, 128.88, 128.45, 127.54, 127.31, 126.52, 126.32, 126.17, 119.17, 114.62, 108.47, 98.83, 60.01, 58.31, 55.24, 33.49, 14.83. IR: 3340, 2921, 1650, 1587, 1490, 1373, 1317, 1248, 1064, 802, 699. m.p.: 200-202 ºC.

RESULTS AND DISCUSSION

The particle size of nano-cellulose and nano-$TiCl_2$/cellulose were investigated by field emission scanning electron microscopy (FESEM) and transmission electron microscopey (TEM) in which the dimensions of catalyst was achieved below 50 nm (Fig. 1).

Comparison of nano-$TiCl_2$/cellulose with nano-cellulose and $TiCl_4$ was achieved by FT-IR spectra (Fig. 2). C-O-Ti stretching band is appeared in 828 cm^{-1} in FT-IR spectrum of nano-$TiCl_2$/cellulose.

Presence of Ti and Cl in catalyst was approved by EDS analysis data (Fig. 3). The percentage of Ti and Cl in $TiCl_4$ are 25.24 and 74.76, respectively. Thus, the amounts of Ti and Cl in EDS data (Ti: 20.3%, Cl: 14.9%) showed the absence of any no reacted $TiCl_4$ in catalyst. So, XRF analysis of nano-$TiCl_2$/cellulose was performed to

Table 1. Results of XRF Analysis of Nano-$TiCl_2$/cellulose and Pure Samples NaCl and TiO_2

Elemental component	$TiCl_4$/nano-cellulose		NaCl		TiO_2	
	KCPS	wt%	KCPS	wt%	KCPS	wt%
Cl	123.5	6.8	516.5	62.4		
TiO_2	464.3	22.2			2318.4	99.1
CO_2	1.6	67.1				
CaO	37.6	1.9				
SiO_2	7.1	1.43				
Al_2O_3	2.3	0.558				
SO_3	5.3	0.504				
MgO	1.9	0.374				
Total		100.86				

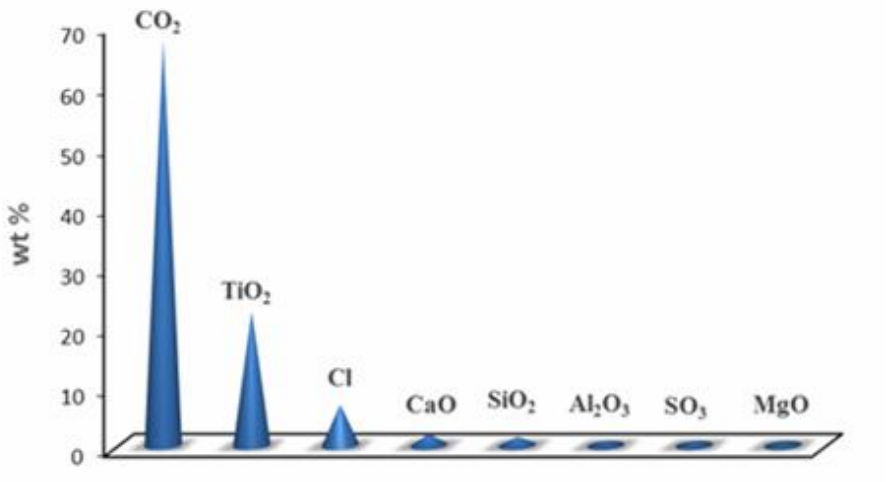


Fig. 4. XRF analysis of nano-$TiCl_2$/cellulose.

determine its elemental component (Table 1, Fig. 4).

To obtain the Ti:Cl ratio in nano-$TiCl_2$/cellulose using XRF analysis, Killo Counts Per Seconds (KCPS) values of elements in catalyst were compared with KCPS values of the same elements in pure samples, NaCl and TiO_2. Through this comparison, the amounts of Ti and Cl were obtained 12.02 g (0.25 mol) and 14.3 g (0.4 mol), respectively. Thus,

The X-ray diffraction (XRD) patterns of nano-$TiCl_2$/cellulose and nano-cellulose are compared in Figure 5. According to this comparison, signals in 2Θ, 20.55 and 34.63, can prove the bonding of Ti to cellulose backbone.

According to the above mentioned data, we have proposed a structure for nano-$TiCl_2$/cellulose (Fig. 6). This catalyst does not need special precautions for preparation,

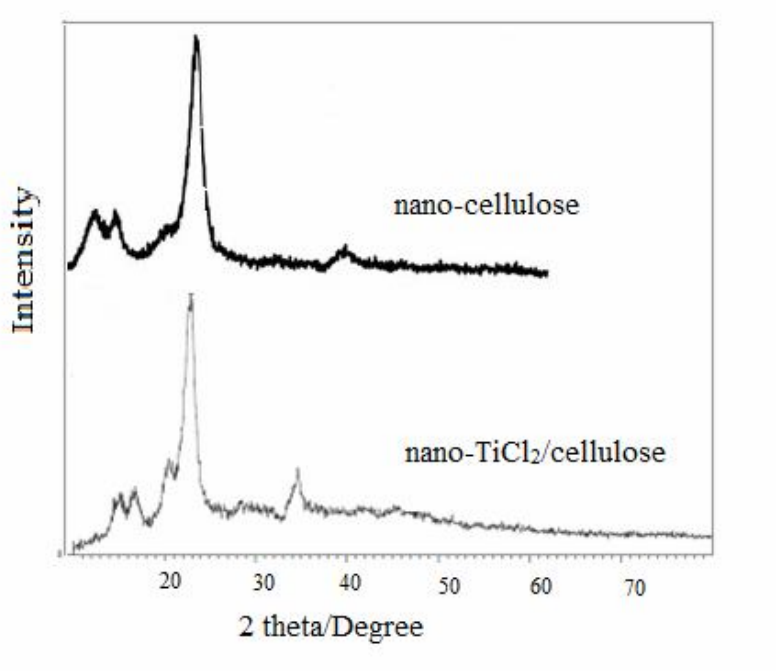


Fig. 5. XRD patterns of nano-$TiCl_2$/cellulose and nano-cellulose.

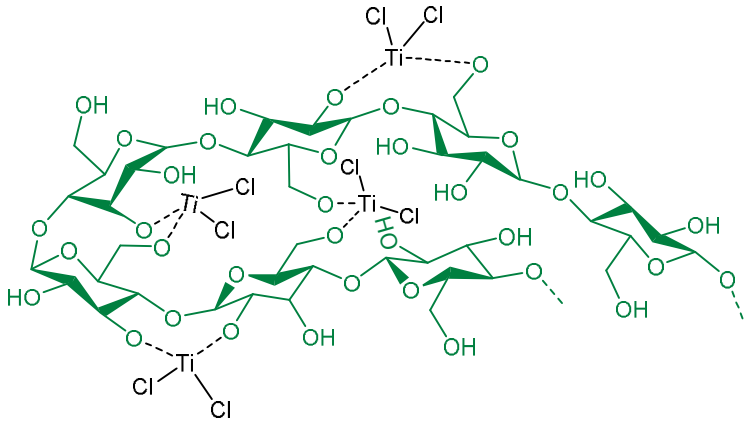
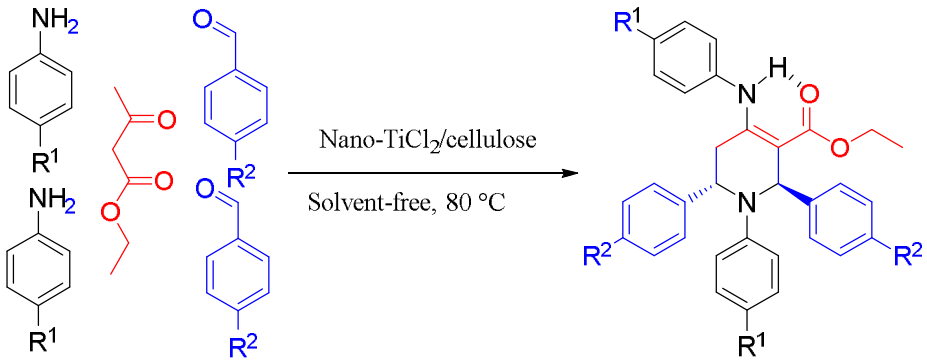


Fig. 6. Proposed structure of $TiCl_4$/nano-cellulose.

handling or storage, and can be stored at an ambient temperature for months without losing its catalytic activity. In continuation of our efforts about application of the supported Lewis acids in organic synthesis, we have used nano-$TiCl_2$/cellulose for preparation of highly functionalized tetrahydropyridines.

THPs were prepared *via* a five-component reaction of *para*-substituted anilines (2 mmol), ethyl acetoacetate (1 mmol), and *para*-substituted benzaldehydes (2 mmol) under solvent-free condition (Scheme 1).

In order to optimize the reaction conditions and to achieve the highest yields, the model reaction of 4-ethylaniline, ethyl acetoacetate and 4-chlorobenzaldehyde was initially carried out under different conditions in the



Scheme 1. Synthesis of THPs catalyzed by nano-$TiCl_2$/cellulose

Table 2. The Reaction of 4-Chlorobenzaldehyde, 4-Ethylaniline, and Ethylacetoacetate in the Presence of Nano-$TiCl_2$/cellulose under Various Conditions[a]

Entry	Solvent	Catalyst (g)	Condition	Time (h)	Yield (%)[b]
1	-	Nano-$TiCl_2$/cellulose (0.05)	R. T (grinding)	5	38
2	-	Nano-$TiCl_2$/cellulose (0.05)	60 °C	4	50
3	-	Nano-$TiCl_2$/cellulose (0.05)	70 °C	4	75
4	-	Nano-$TiCl_2$/cellulose (0.05)	80 °C	4	85
5	-	Nano-$TiCl_2$/cellulose (0.05)	100 °C	4	70
6	H_2O	Nano-$TiCl_2$/cellulose (0.05)	Reflux	5	50
7	EtOH	Nano-$TiCl_2$/cellulose (0.05)	Reflux	5	47
8	MeOH	Nano-$TiCl_2$/cellulose (0.05)	Reflux	5	40
9	THF	Nano-$TiCl_2$/cellulose (0.05)	Reflux	5	58
10	CH_3CN	Nano-$TiCl_2$/cellulose (0.05)	Reflux	5	30
11	-	Nano-$TiCl_2$/cellulose (0.04)	80 °C (Grinding)	4	90
12	-	Nano-$TiCl_2$/cellulose (0.03)	80 °C (Grinding)	4	93
13	-	Nano-$TiCl_2$/cellulose (0.02)	80 °C (Grinding)	4	75
14	-	-	80 °C (Grinding)	8	30
15	-	Nano-$TiCl_2$/cellulose (0.03), 2nd run	80 °C (Grinding)	7	65
16	-	Nano-$TiCl_2$/cellulose (0.03), 3rd run	80 °C	12	60
17	-	Nano-$TiCl_2$/cellulose (0.03), 4th run	80 °C	12	50

[a]Reaction condition: 4-chlorobenzaldehyde (2 mmol), 4-ethylaniline (2 mmol) and ethylacetoacetate (1 mmol). [b]Isolated yield.

Table 3. Comparative Study of the Present Method and some other Reported Methods for the Synthesis of Highly Functionalized Tetrahydropyridines

Entry	Solvent	Catalyst (g)	Condition	Time (h)	Yield (%)[a]
1[b]	EtOH	$ZrCl_4$ (0.15 mmol)	R. T (grinding)	16	86 [3]
2[c]	EtOH	$ZrOCl_2.8H_2O$ (20 mol%)	Reflux	3	86 [15]
3[b]	EtOH	$Fe(NO_3)_3.9H_2O$ (20 mol%)	R. T	7	88 [17]
4[b]	MeOH	$FeCl_3/SiO_2$ NPs (0.8 mol%)	Reflux	7	86 [18]
5[b]	-	HOAc (5 ml)	R. T	7	85 [20]
6[d]	EtOH	$PTSA.H_2O$ (0.11 g)	R. T	12	88 [16]
7[d]	CH_3CN	CAN (15 mol%)	R. T	35	68 [14]
8[d]	CH_3CN	L-Proline/THF (20 mol%)	30 °C	22	75 [5]
9[d]	-	Nano-$TiCl_2$/cellulose (0.03)	80 °C	2	86

[a]Isolated yield. [b]Benzaldehyde, 4-methylaniline and ethyl acetoacetate were used. [c]Benzaldehyde, 4-methylaniline and methyl acetoacetate were used. [d]Benzaldehyde, 4-chloroaniline and ethyl acetoacetate were used.

Table 4. The Reaction of Various *Para*-substituted Anilines and Ethyl Acetoacetate with *Para*-substituted Benzaldehydes in the Presence of Nano-$TiCl_2$/cellulose[a]

Entry	R^1	R^2	Product	Time (h) /Yield (%)[b]	M.P. (°C)
1	H	Br	IV_a	2/76	218-220[25]
2	Me	H	IV_b	2/81	193-194[17]
3	Me	Br	IV_c	3/85	215-217
4	Et	Cl	IV_d	4/93	209-211
5	Cl	H	IV_e	2/86	202-204[26]
6	Cl	Cl	IV_f	3/83	214-215[27]
7	Br	Cl	IV_g	4/82	193-195[25]
8	Br	OMe	IV_h	2/82	217-219[28]
9	H	Me	IV_i	3/75	228-230[29]
10	H	Cl	IV_j	3/76	202-204[25]
11	Me	Me	IV_k	3/85	170-172[17]
12	Et	H	IV_l	2/79	187-189
13	Et	Me	IV_m	3/85	176-178
14	Br	H	IV_n	2/84	200-202[17]

[a]Reaction conditions: *para*-substituted anilines (2 mmol), ethyl acetoacetate (1 mmol), *para*-substituted benzaldehydes (2 mmol), catalyst (0.03 g), solvent-free/80 °C. [b]Isolated yield.

presence of nano-$TiCl_2$/cellulose. The results are presented in Table 2. To investigate the effect of reaction temperature, the reaction was performed initially in solvent-free condition at various temperatures (Table 2, entries 1-5). As it is observed, the best result was obtained at 80 °C (Table 2, entry 4). The effect of solvent was also investigated by performing the model reaction in various solvents including H_2O, EtOH, MeOH, THF and CH_3CN (Table 2, entries 6-10). The model reaction gave the highest yield in solvent-free condition.

To optimize the catalyst amount, the model reaction was performed in the presence of various amounts of the catalyst and according to the obtained results (Table 2, entries 11-13) 0.03 g of the catalyst was chosen as the best catalyst amount. The reusability of the catalyst was examined and the obtained results showed that the reactivity of the catalyst decreases for the next run. (Table 2, Entries 15-17).

Comparison of the nano-$TiCl_2$/cellulose-catalyzed THPs synthesis with previously reported methods shows the merit of the present protocol (Table 3).

Based on the optimized reaction conditions, a range of highly functionalized tetrahydropyridines were synthesized by the reaction of various *p*-substituted anilines, ethyl acetoacetate, and *p*-substituted benzaldehydes in the presence of nano-$TiCl_2$/cellulose under solvent-free condition (Table 4). All compounds were identified by physical and spectroscopic data (mp, FT-IR and ^{1}H NMR). Moreover, the new products were specified through using the aforementioned methods as well as ^{13}C NMR spectroscopy and CHN analysis.

CONCLUSIONS

We have developed a simple and efficient method for the synthesis of highly substituted tetrahydropyridines by one-pot multi-component reactions under solvent-free conditions using nano-$TiCl_2$/cellulose as a green, cheap and biodegradable solid acid catalyst. Environmentally benign conditions, clean synthesis, easy work-up, high yields, solvent-free condition and medium reusability of catalyst are some advantages of this novel methodology.

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